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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,665	05/03/2001	Ute Rogner	03495.0203	6991

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1647	15

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/847,665	Applicant(s) Rogner et al
	Examiner Robert C. Hayes, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 4, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-7, 9, 10, 15-20, 22, 24-28, 33-41, 45-49, and 54-61* is/are pending in the application.

4a) Of the above, claim(s) *1-3, 5-7, 9, 10, 20, 27, 28, 35-39, 45, 49, 54, 55,* 59 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *15-19, 22, 24-26, 33, 34, 40, 41, 46-48, 56-58, 60, and 61* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-3, 5-7, 9, 10, 15-20, 22, 24-28, 33-41, 45-49, and* 54-61 are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s). _____
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____	6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group III (claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58 & 60-61; as it relates to SEQ ID NO:4 - the human Nap1L2 promoter, versus any different promoter, for example, as in claims 20, 35-36 & 59) in Paper No.10 is acknowledged. (Note that claim 26 is being interpreted as a method of making a transfected cell, versus *in situ* modifying a NAP1L2 or Nap1l2 gene in a cell, which is a different restrictable invention). The traversal is on the ground(s) that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions", as it relates to various recited cell lines and "wild type animals". However, in contrast, the elected claims alternatively are directed toward polynucleotides transfected into neural host cells, where the source from which such transfected host cells are "derived" carries no patentable weight. In other words, neural cells are neural cells, and therefore, the species election is withdrawn. Note further that Applicants' arguments are directed toward the species election, which has been withdrawn and which is separate from the remaining restriction requirement. Second, Applicants' conclusion that "the restriction requirement be withdrawn and all the pending claims be considered together" is not persuasive, because these other distinct inventions require different starting materials, administration protocols and different goals, which would therefore constitute a serious burden on the examiner for searching and examining these distinct inventions, and for the reasons made

of record in Paper No: 9. Thus, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-3, 5-7, 9-10, 20, 27-28, 35-36, 37-39, 45, 49, 54-55 & 59 (and claims not related to the human Nap1L2 promoter sequence of SEQ ID NO:4) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No.10.

This application contains claims 1-3, 5-7, 9-10, 20, 27-28, 35-36, 37-39, 45, 49, 54-55 & 59 (and claims not related to the human Nap1L2 promoter sequence of SEQ ID NO:4) drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 U.S.C. § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15-19, 22, 24, 34, 40, 46, 48, 56-58 & 60-61 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. For example, the current recitation of "[a] recombinant polynucleotide" or "polynucleotide" encompasses all

naturally occurring polynucleotides/gene sequences which normally undergo recombinational repair; thereby, not necessarily involving the hand of man to isolate or purify the polynucleotide. It is suggested that amending claims 15, 16, 24 & 45 to "an isolated polynucleotide..." should obviate this rejection.

In addition, the recitations of "a neural/eukaryotic cell" or "recombinant neural cell" encompass a human organism. It is suggested that amending claims 18, 34, 40, 48 & 57 to "an isolated neural/eukaryotic cell" should obviate this rejection.

3. Claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58 & 60-61 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

The specification asserts (e.g., page 3 of the specification), "that *Nap112* plays an essential role in the development of the nervous system and suggests a putative role for it in the control of cell proliferation and differentiation processes, [and that] [a]berrant cell cycle regulation and differentiation may, therefore, be one of the mechanisms underlying neural tube defects (NTDs)". Page 9 of the specification also proposes that "[t]he change in proliferating cells can be a control of cancer". However, because many genes are reasonably involved in "development of the nervous system and... [have] a putative role... in the control of cell proliferation and differentiation processes", or in the 'control of cancer", and/or may "identify predisposition to developmental defects", no specific utility exists for the instant claimed gene

sequences, because no specific biological activity nor specific "developmental defect" is described within the specification that is specifically associated with any nucleic acid transcribed by the promoter polynucleotide sequence of SEQ ID NO:4; especially as it relates to claims directed toward "at least one modification... that causes a loss of biological activity" (i.e., as it relates to claims 15, 22, 26, 36 & 60-61).

Likewise, the claimed polynucleotides have no substantial utility because further experimentation is necessary at the time of filing the instant invention to attribute a "real world" utility to the claimed recombinant polynucleotides, which the specification fails to specifically describe.

Applicant is directed toward the Revised Interim Utility Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58 & 60-61 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5. Claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58 & 60-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes the murine and human *Nap1l2* polynucleotide sequences of SEQ ID Nos: 2 & 3, respectively. SEQ ID NO:4 is also described as a human *Nap1L2* promoter sequence. No other sequences, allelic variants, or molecules from different species, which "includes at least one modification... that causes a loss of biological activity", "hybridizes under stringent conditions...", "is a chromosome or part of a chromosome", or "comprises [unknown] "heterologous" sequences, or "comprises" such sequences that merely "include... at least 20 nucleotides of SEQ ID NO:4" are described. Nor can one skilled artisan reasonably visualize such polynucleotide sequences with any assayable and functional biological activity (i.e., by SEQ ID NO) based on the limited written description provided in the instant specification. In other words, the genus of such DNA or "gene" sequences, as currently claims, which encompasses unknown 5'-, 3'-flanking, enhancer, additional promoter sequences and other unknown chromosomal sequences, and which would be expected by the skilled artisan to have widely divergent functional properties, does not reasonably meet the written description requirements under 35 U.S.C. 112, first paragraph, because one skilled in the art cannot reasonably visualize or predict what critical nucleotide residues would structurally characterize the genus of polynucleotides currently encompassed by the claims.

Applicant is directed toward the Revised Interim Utility and Written Description Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

6. Claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58 & 60-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a promoter polynucleotide sequence consisting of SEQ ID No: 4, does not reasonably provide enablement for polynucleotides that "include at least one modification... that causes a loss of biological activity", or for any structurally and functionally uncharacterized promoter sequences that merely comprise fragments of SEQ ID NO:4, or merely comprise hybridization products with no known structural nor recited functional characteristics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims do not recite, nor require, any functional embodiments for the claimed invention. Moreover, the skilled artisan know not reasonably know what critical nucleotide sequences results is a functional promoter in any cell; especially as it relates to claims merely directed toward fragments of SEQ ID NO:4, "loss of biological function", or for hybridization products thereof, which by themselves would not reasonably be expected to transcribe any functional mRNA encoding an assayable and functional polypeptide without requiring undue experimentation to discover such after-the-fact. Thus, the claims are not enabled because

random mutations to any promoter sequence would be predicted by one of skill in the art to result in an inactive promoter sequence, as taught by LeClerc et al. (1982).

7. Claims 40 & 41 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The appropriate ATCC/ CNCM numbers and required Deposit information critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 U.S.C. §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification lacks sufficient deposit information for the deposit of any plasmid DNA "under the Accession number I-2463, I-2464, I-2465, or I-2466"/ "pBPX1, pBPX2 or pBPX3". Because these undefined genes are unknown, and therefore, publicly not available or can reproducibly isolated from nature without undue experimentation, a suitable deposit for patent purposes is required.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that **all restrictions imposed by the depositor on the availability to the public of the deposited material will be**

irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

8. Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is ambiguous and unknown what exactly the recitations, "plasmid pBPX1 or pBPX2 or pBPX3" entail, or what "insert" is being referenced; especially in that the specification fails to identify such. In other words, Applicants should amend the claim to indicate what SEQ ID NO is contained in the appropriate deposited plasmid; as well as amend the specification on page 44 to indicate the appropriate SEQ ID NOs being represented by each of these designations, in order to further comply with the SEQUENCE RULES.

9. Claims 24 & 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unknown what metes and bounds "stringent hybridization conditions" entail, in that it is unknown whether low, moderate or high stringent conditions are envisioned; nor what exactly defines these conditions, which is further not recited in the claims.

10. Claims 19 & 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because neural cells are neural cells, and not "derived from an immortal cell line...[or a] tumor derived cell line"; thereby, being indefinite (i.e., as it relates to claims 19 & 58). In addition, because it is patentably immaterial from where a neural host cell is derived, it is unclear what exactly is intended by these claims for using such claim language.

11. Claims 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Polynucleotides cannot "further comprise a heterologous *amino acid* sequence...", by definition; thereby, making the claim indefinite.

12. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: transfecting the cell with a vector containing the appropriate polynucleotide. Alternatively, when or how the step of "selecting the modified cells" occurs is not recited; thereby, being incomplete.

Note again, that amending this claim to different methods related to *in situ* modification a Napl1L2 gene, etc. will necessitate this claim being withdrawn as being drawn to a nonelected invention.

Claim Rejections - 35 U.S.C. § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 17, 24-25 & 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al. (clone EST27025; Accession no. AA324132; April, 1997).

Adams et al. teach an isolated human 5' DNA clone, whose sequence is deposited with the GenBank/EMBL database, which contains "at least one modification... selected from a) substitution, b) deletion, c) frameshift, d) insertion, or e) site-directed mutagenesis that

[therefore, inherently] causes a loss of biological function in the NAP1L2 gene" (i.e., as it relates to SEQ ID NO:4). In that Adams DNA inherently is "part of a chromosome", "hybridizes under stringent conditions with SEQ ID NO:4", and "comprises... at least 20 nucleotides of SEQ ID NO:4, the limitations of claims 17 & 24 are anticipated. In that Adams' DNA was cloned into a vector and grown in *E.coli* host cells, the limitations of claims 25 & 33 are also met.

It is noted that the above rejection is based in part upon a disclosure provided in a computer database record. Because the database was indexed so as to be available to the relevant part of the public, it is considered to be a U.S.C. § 102; see *In re Wyer*, 210 USPQ 790.

14. Claims 15-17, 24-25, 33, 40-41 & 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (clone bWXD759; Accession no. AC004074; Jan. 1998).

Chen et al. teach an isolated human DNA clone from the X chromosome, whose sequence is deposited with the GenBank/EMBL database, which is 100% identical to SEQ ID NO:4; thereby, being also inherently "part of a chromosome", "hybridizes under stringent conditions with SEQ ID NO:4", and "comprises... at least 20 nucleotides of SEQ ID NO:4 (i.e., as it relates to claims 16, 17, 24 & 56). In that this human DNA clone was reasonably inserted into a vector, grown in eukaryotic cells, and otherwise appears identical to one of the pBPX plasmids deposited at the C.N.C.M., the limitations of claims 25, 33 & 40-41 are anticipated. Lastly, in that the NAP1L2 gene is deleted, the limitations of contains "at least one modification... selected from a) substitution, b) deletion, c) frameshift, d) insertion, or e) site-directed mutagenesis that

[therefore, inherently] causes a loss of biological function in the NAP1L2 gene" is met (i.e., as it relates to claims 15 & 17).

It is noted that the above rejection is based in part upon a disclosure provided in a computer database record. Because the database was indexed so as to be available to the relevant part of the public, it is considered to be a U.S.C. § 102; see *In re Wyer*, 210 USPQ 790..

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
April 28, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600